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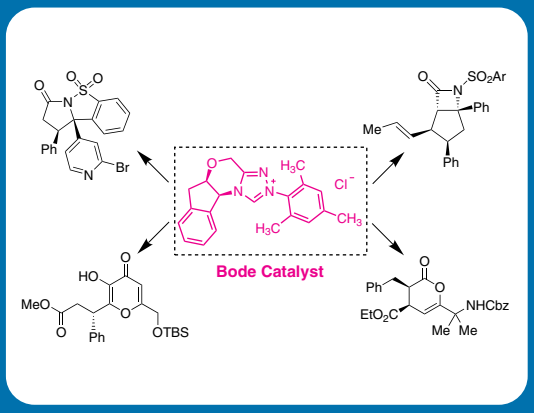

CONTENTS

Contribution

N-Mesityl Substituted Chiral Triazolium Salts: Opening a New World of N-Heterocyclic Carbene Catalysis

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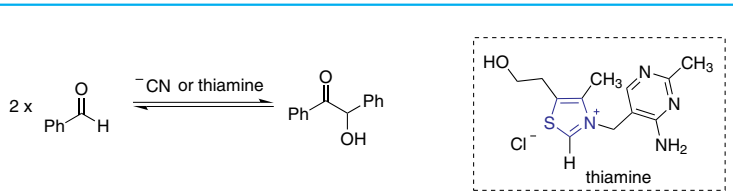
1. Introduction

The dimerization of aldehydes to form benzoins (**Scheme 1**) is one of the oldest known organic reactions, first reported in 1832 by Liebig.[1] The original cyanide catalyzed benzoin reaction was long appreciated for its simplicity and mechanistic intricacies but offered few useful synthetic applications.[2] The discovery by Ukai[3] in 1943 that the essential co-factor thiamine, or vitamin B1, catalyzes the benzoin reaction provided a key clue to understanding a broad range of thiamine-dependent enzymes and reinvigorate interest in this class of reactions.[4] The use of ylides derived from thiamine, which are now classified as N-heterocyclic carbenes,[5] led to both new reactions, such as the Stetter addition of aldehydes to electron-deficient olefins,[6] and new catalysts types inspired by the chemistry of the thiazolium salt at the heart of thiamine.[7] Key to the success of thiamine and its relative is the catalytic generation of an acyl anion equivalent.[8] Typical procedures for the preparation of this reactive species would require harsh conditions and intricate protecting group strategies. With thiamine catalysis, this reactive species can be generated under aqueous and nearly neutral conditions.

By the year 2003, modern, enantioselective versions of the benzoin and certain Stetter reactions had emerged, driven by the design and preparation of new chiral azolium salts. Pioneering work by Knight and Leeper,[9] Enders,[10] and Rovis[11] had converged on the use of chiral, bicyclic triazolium salts as the ideal platform for N-heterocyclic carbene catalysts capable of inducing highly enantioselective reactions including intermolecular homo-benzoin reactions,[12] intramolecular Stetter reactions,[13] and intramolecular aldehyde–ketone crossed benzoin reactions.[14] These methods are now well established and widely employed for the enantioselective synthesis of complex molecules including bioactive natural products.[15]



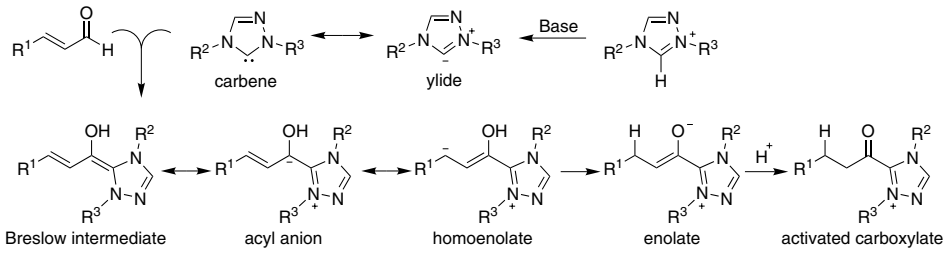
Scheme 1. Benzoin reaction with benzaldehydes.

2. NHC-Catalyzed Reactions of α-Functionalized Aldehydes

In late 2003, then at the University of California–Santa Barbara, we initiated a research program aimed at employing N-heterocyclic carbenes as catalysts for the formation of other reactive species. We recognized the combination of an N-heterocyclic carbene catalysts with an α-functionalized aldehyde, such as an α,β-unsaturated aldehyde or an α-halo aldehyde, could result in the generation of reactive species including homoenolate equivalents, enolate equivalents, and acyl azoliums, which serve as activated carboxylates (**Scheme 2**).

Within two years of our initial studies, we had developed catalysts and conditions that allowed for the selective formation of each of these reactive intermediates, making possible an entirely new class of catalytic reactions. Key to the success of this research program, and the vast number of new enantioselective transformations that it has enabled, was our recognition that *N*-mesityl substituted triazolium salts are critical for high reactivity and selectivity in N-heterocyclic carbene catalyzed reactions of α-functionalized aldehydes. Our initial studies, completed in 2005, identified achiral *N*-mesityl substituted catalyst **A** as the minimal structure required for the generation of these reactive intermediates under mild conditions.[16] In the following year, we disclosed chiral *N*-mesityl substituted triazolium salts **B** and ***ent*-B**.[17]

By developing an efficient synthetic route to incorporate the essential *N*-mesityl substitution, we are able to produce **B** on a preparative scale at modest cost. This catalyst promotes a large number of highly enantioselective transformations, otherwise not effected via other chiral azolium salts lacking an *N*-mesityl or related substitutent. These reactions and their scope are highlighted in the review below (**Scheme 3**).



Scheme 2. Reactive species generation from α,β-unsaturated aldehyde with N-heterocyclic carbene.

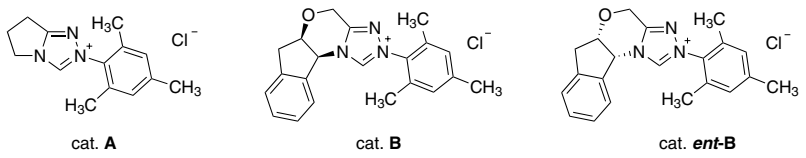
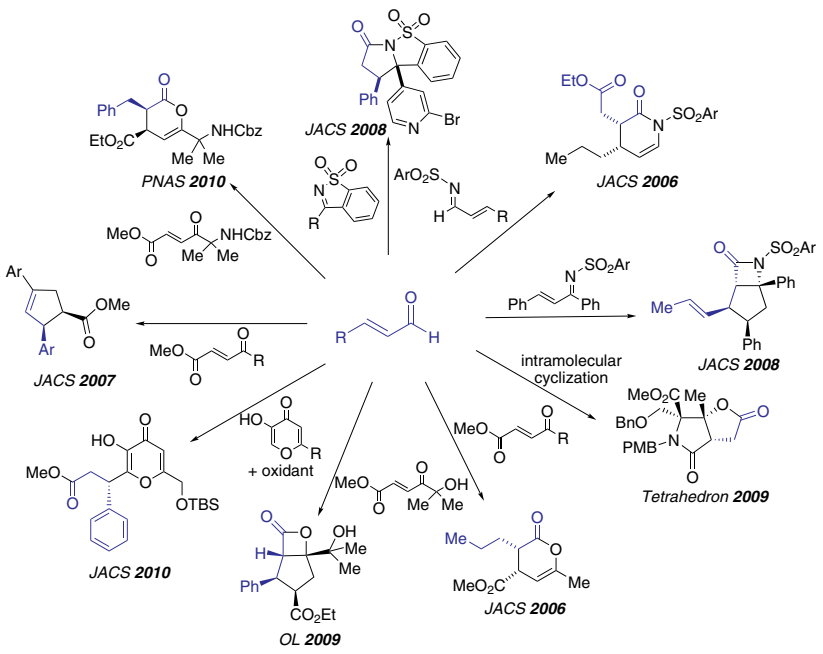


Chart 1. Achiral *N*-mesityl substituted catalyst **A**, chiral catalysts **B** and ***ent*-B**.



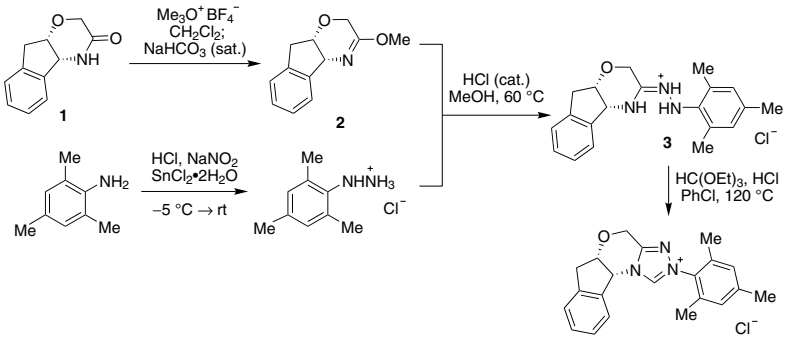
Scheme 3. Reactions promoted by chiral catalysts **B** and ***ent*-B**.

3. Catalyst Synthesis and Counterion Effects

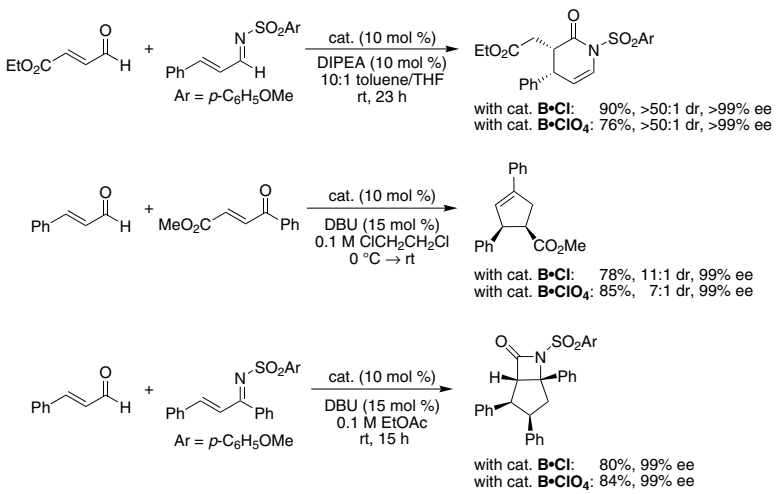
Our catalyst design borrows its chiral elements on the outstanding work of Knight and Leeper,[9] who first reported chiral triazolium salts derived from 1,2-amino alcohols, and of Rovis,[11] who first employed the readily available 1,2-aminoindanol for chiral azolium salts. In both cases, high quality *N*-mesityl-hydrazine hydrochloride is needed. While this is commercially available the cost is prohibitive for large scale syntheses. We have therefore devised a reliable procedure for the large scale preparation of this hydrazine salt from the corresponding aniline. Although yields are not high (36−40% yield), it can be execute on a 1 mol scale with inexpensive starting materials and without the need for chromatography or distillation.

The preparation of the chiral catalysts begins by following the work of Rovis, who has prepared aminoindanol derived triazoliums bearing different aromatic substituents.[13] Lactam **1** is converted to the imidate **2** with trimethyloxonium tetrafluoroborate and condensation with *N*-mesityl hydrazine affords **3** (**Scheme 4**). The most challenging step is the final ring closing, which fails or gives low yields under the previously developed conditions. Our modified procedures uses lower temperatures and HCl or $HClO_4$ to promote the ring closure. The resulting chloride or perchlorate salts are readily isolated and stored.[18]

In all cases examined to date, the counterion plays no role in the reaction outcome. Thus catalysts of type **A** or **B** bearing chloride, perchlorate or tetrafluoroborate counterions give identical yields and enantioselectivities provided that at least a catalytic amount of base is used in the reactions (**Scheme 5**).[19] The only discernable difference is that the chloride catalysts are somewhat more hydroscopic but this does not generally affect the reaction outcome.



Scheme 4. Synthesis of chiral triazolium catalyst ***ent*-B**.

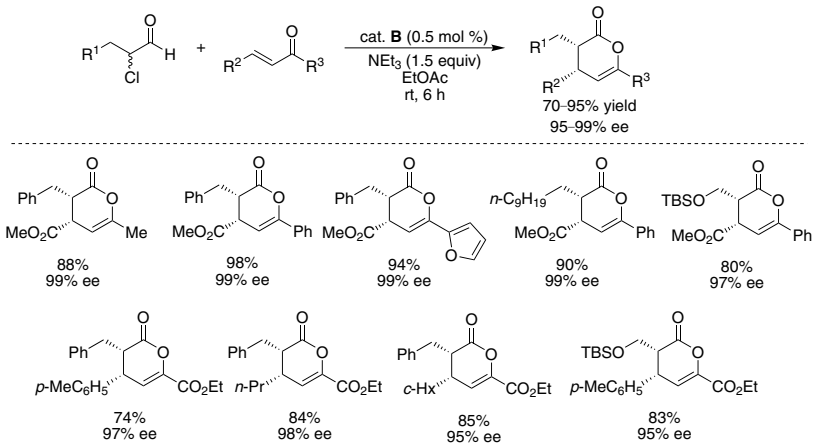


Scheme 5. In the presence of bases, there is no significant effect of the azolium counterions. (DIPEA = *N*,*N*-diisopropylethylamine, DBU = 1,8-diazabiyclo[5.4.0]undec-7-ene)

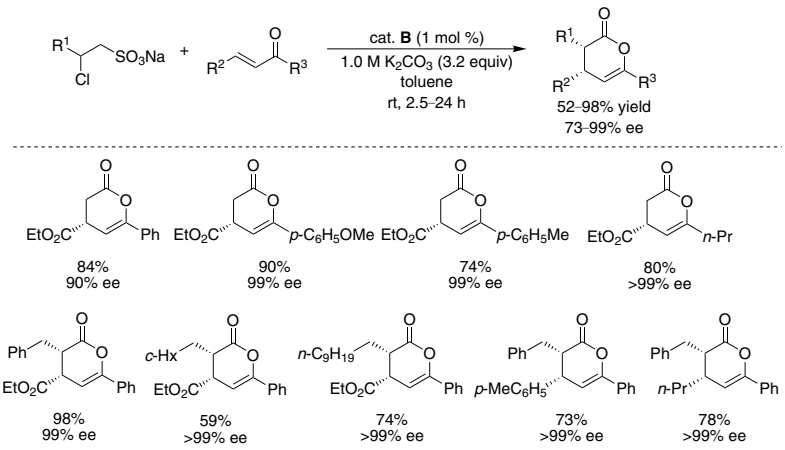
4. Hetero-Diels–Alder Reactions

The catalytic generation of ester enolate equivalents under mild, simple conditions that allow for enantioselective reactions has been a long held goal of synthetic organic chemistry. In 2006, we disclosed the use of *N*-mesityl substituted triazolium salts for the catalytic generation of ester enolate equivalents from α-halo- and α,β-unsaturated aldehydes.

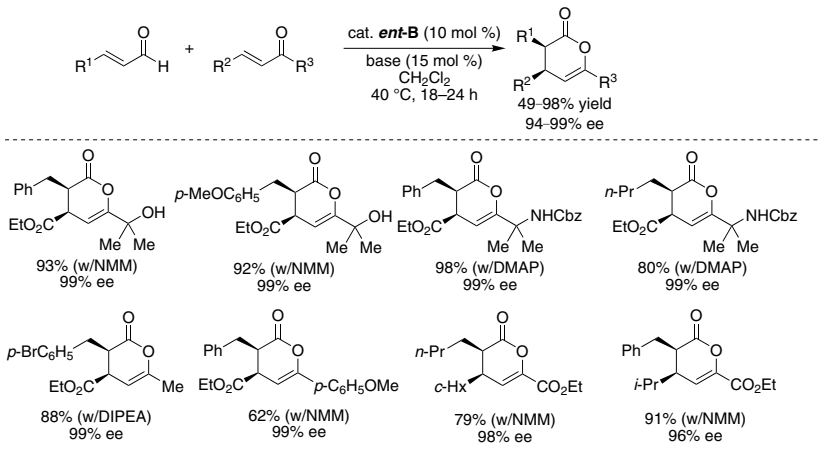
Racemic α-halo aldehydes undergo highly enantioselective annulations with electron deficient oxo-dienes under remarkably mild and simple reaction conditions (**Scheme 6**).[20] Due to the high reactivity of these substrates, only 0.5 mol% of chiral triazolium salt **B** is needed for excellent yields and enantio-selectivities. The racemic α-halo aldehydes undergo epimerization in the reaction conditions rending this reaction



Scheme 6. Diels–Alder reactions of α-chloroaldehydes with oxodienes.



Scheme 7. Diels–Alder reactions with α-chloroaldehyde bisulfite salts.



Scheme 8. Diels–Alder reactions with α,β-unsaturated aldehydes. (NMM = *N*-methylmorpholine, DMAP = 4-(dimethylamino)pyridine)

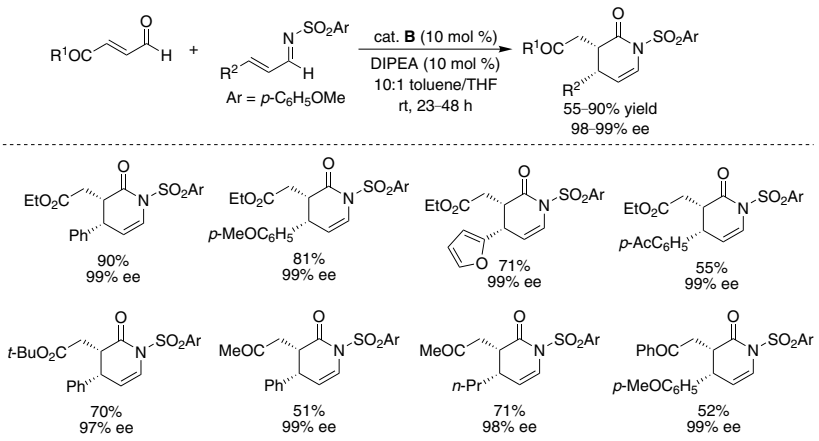
an enantio-convergent process. The scope of this process is outstanding, with either aromatic or aliphatic substuents tolerated by both reaction partners.

The α-halo aldehyde starting materials are readily prepared in a single step from the corresponding aldehydes. They have, however, limited shelf life. We have therefore developed conditions for isolating and storing them as their bisulfite adducts and developed biphasic reaction conditions for the use of these convenient starting materials directly in the enantioselective annulation reactions (**Scheme 7**).[21] Similarly high yields, enantioselectivities, and substrate scope are observed even under aqueous conditions. Importantly, this procedure works well with the commercially available bisulfite adduct of chloroacetaldehyde, making possible enantioselective acetate additions without the need to prepare the toxic and potentially explosive α-chloroaldehyde.

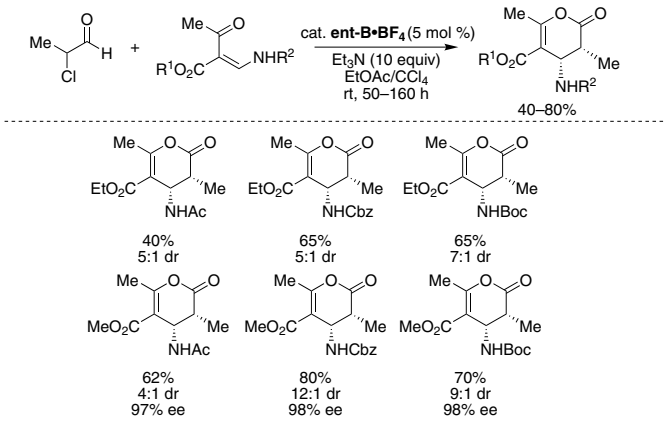
The identical reactive intermediates can be generated from α,β-unsaturated aldehydes and we have recently reported a method for highly enantioselective annulations from both aromatic and aliphatic substituted enals (**Scheme 8**).[22] Under these conditions, high catalysts loadings are needed due to the fact that only a trace amount of the active carbene catalysts is generated by the weak bases. This procedure also expands the scope of the annulations to include α-hydroxy- and α-aminoenones that give products bearing valuable synthetic handles for further transformations. Scheidt has also applied these chiral catalysts to an intra-molecular variant of this reaction.[23]

The heterodiene can also be extended to nitrogen analogues using either α-chloroaldehydes or commercially available electron-deficient enals as the enolate precursors (**Scheme 9**).[17] This procedure affords *cis*-disubstituted dihydropyridinones in good yields and with outstanding enantioselectivities.

Recently, several other groups have used our catalyst and conditions for even more complex hetero-Diels–Alder reactions. An excellent example is that of Kobayashi and coworkers, who reported the formation of amine-substituted products by reactions of α-haloaldehydes and vinylogous amides (**Scheme 10**).[24]



Scheme 9. Azadiene Diels–Alder reactions using α,β-unsaturated aldehydes.



Scheme 10. Enantioselective synthesis of dihydropyranones.

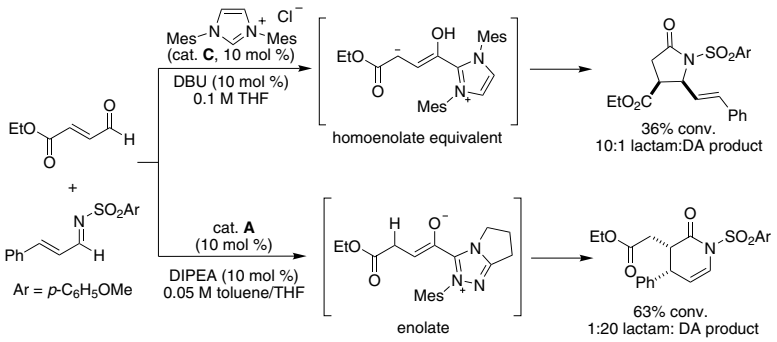
5. Catalytic Generation of Homoenolate Equivalents

The nature of the azolium catalyst employed in the annulation reactions plays an important role in the type of reactive intermediate generated. α,β-Unsaturated aldehydes can access either the homoenolate or enolate pathways. In general, the enolate pathway is favored by the use of weak bases (DMAP or NMM) and triazolium catalysts, while stronger bases (DBU) and imidazolium-derived N-heterocyclic carbenes prefer the homoenolate equivalent route. Reactions that proceed via the homoenolate pathway generate five-membered ring products such as γ-lactams, γ-lactones, or cyclopentane derivatives. For example, the same substrates shown in **Scheme 11** give either γ-lactams or dihydropyridinones depending on the catalyst type.[17]

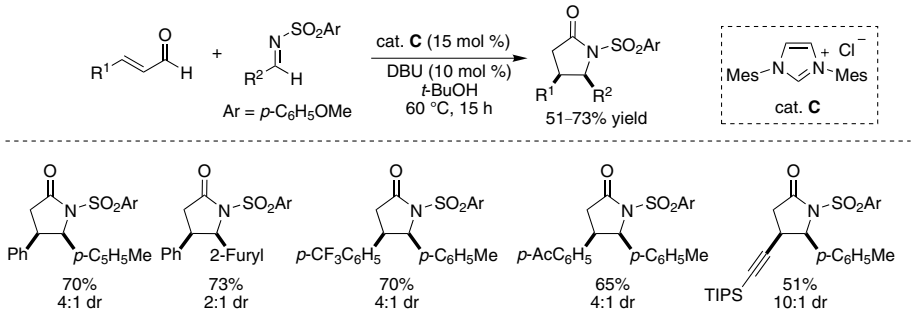
In general, imidazolium-derived catalysts are superior to triazolium-derived variants for γ-lactone[25] and γ-lactam[26] formation, with commercially available IMesCl (cat. **C**, CAS Nr. 141556-45-8) as the best achiral catalysts for many of these transformations (**Scheme 12**).

For certain highly reactive electrophiles, *N*-mesityl substituted triazolium salts are also active. The actual reaction mechanisms may be more complex in these cases, but the products are those derived from formal homoenolate generation and addition. Several such examples are listed below.

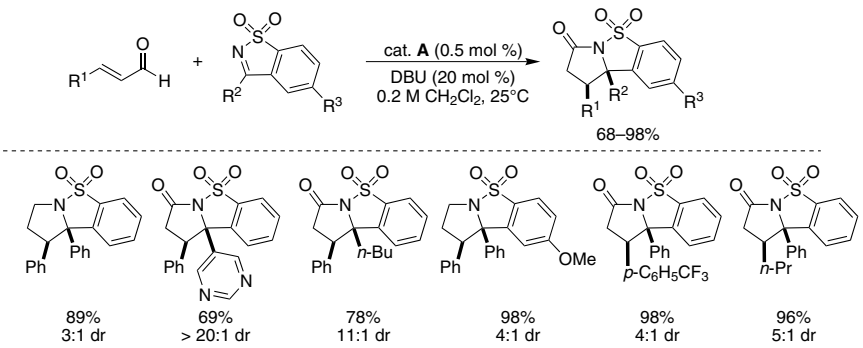
Saccharine derived-cyclic ketimines are unexpectedly good electrophiles in NHC-catalyzed annulations with enals using achiral triazolium salt **A** (**Scheme 13**).[27] These reactions demonstrate broad scope in both the enal and ketimine reaction partner and afford unique polycyclic products in excellent yield and with low catalysts loading. Although chiral triazolium salt **B** is also an excellent catalyst for this reaction, enantioselectivities are relatively modest. This reflects the known difficulty of effecting highly enantioselective reactions that proceed via the homoenolate pathway.



Scheme 11. Catalyst effects with α,β-unsaturated aldehydes and imines.



Scheme 12. γ-Lactam formation promoted by IMesCl (cat. **C**).

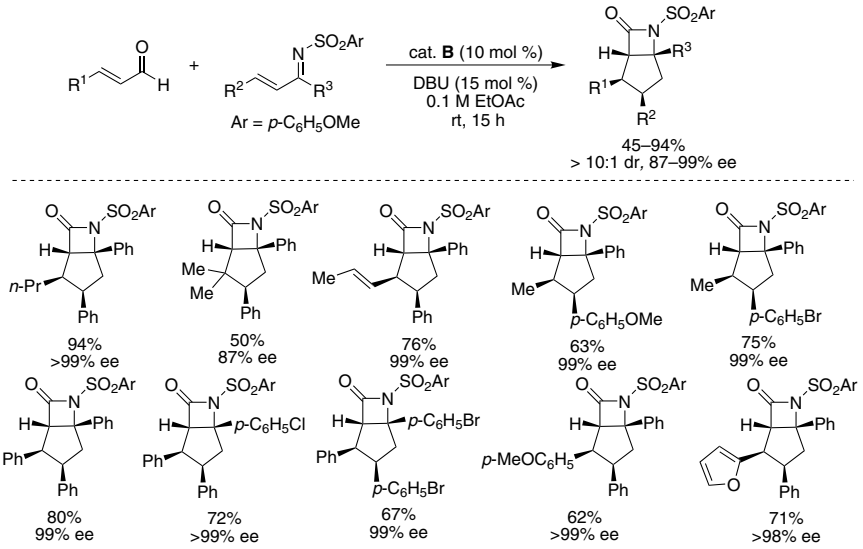


Scheme 13. Homoenolate additions of saccharine derived-cyclic ketimines.

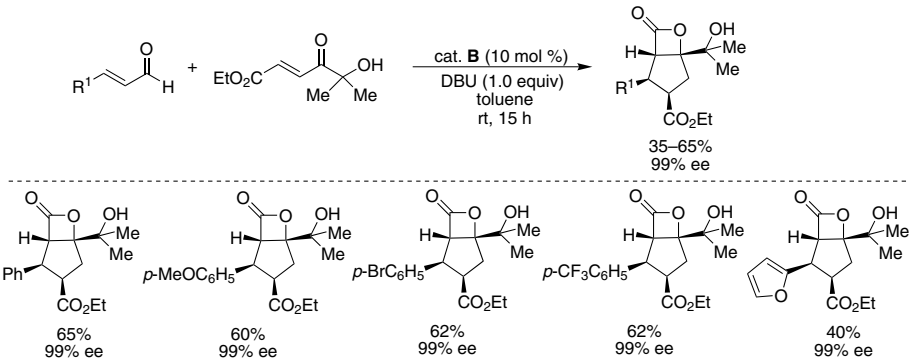
When α,β-unsaturated *N*-tosyl ketimines are used as substrates, bicyclic β-lactams, rather than γ-lactams are formed (**Scheme 14**).[28] This reaction is most easily thought of as a conjugate addition of the homoenolate derived from the α,β-unsaturated aldehyde followed by ring-closing reactions, although the actual reaction mechanism probably involves a different pathway. This remarkable cascade process affords enantiopure β-lactams in excellent yields and stereoselectivities.

A similar reaction for the formation of enantiopure cyclopentyl β-lactones is also possible with the same catalyst and unsaturated aldehydes (**Scheme 15**).[29] In this case, the use of α'-hydroxyenones is essential and provides a useful synthetic handle for the elaboration of the products.

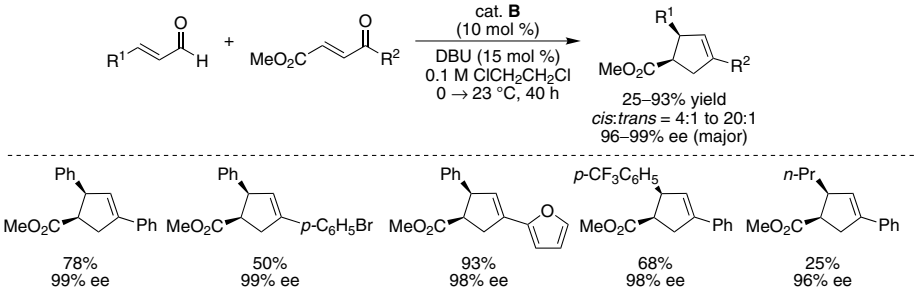
With enones bearing an aromatic group, the initial β-lactone products undergo spontaneous decarboxylation to afford disubstituted-cyclopentenes (**Scheme 16**). The overall reaction allows the combination of an enal and a simple enone to give enantioenriched cyclopentenes in a single step and under mild, simple reaction conditions.[30]



Scheme 14. Bicyclo-β-lactam annulations.



Scheme 15. Enantiopure bicyclo-β-lactone annulations.



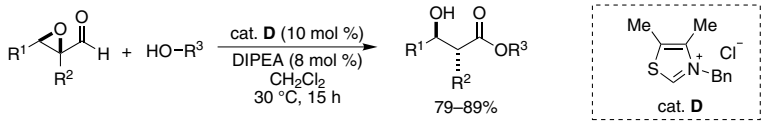
Scheme 16. Enantioselective cyclopentene annulations.

6. Catalytic Generation of Activated Carboxylates

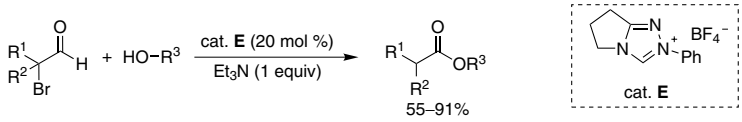
In all of the reactions noted above, catalyst turnover is affected by the formation of an acyl azolium species that undergoes a lactonization or lactamization reaction. These acyl azolium intermediates therefore serve as catalytically generated activated carboxylates and can be used for esterification and amidation reactions. By choosing the appropriate substrates, N-heterocyclic carbene catalysts can effect both esterifications and amidations under catalytic conditions that do not require coupling reagents or produce chemical waste.

The first reports on the catalytic generation of acyl azoliums for esterification reactions utilized simpler azolium salts. In 2004, our group reported the diastereoselective opening of α,β-epoxyaldehydes with simple thiazolium-derived ylides (**Scheme 17**).[31] The *N*-mesityl substituted triazolium salt **A** also catalyzes this reaction and is in many cases the superior reagent. Rovis, also in 2004, reported the generation of acyl azoliums from α-halo aldehydes using *N*-phenyl substituted triazolium salt **E** (**Scheme 18**).[32] Rovis has also described an impressive example of enantioselective protonation using a chiral *N*-pentafluorophenyl substituted triazolium salt.[33]

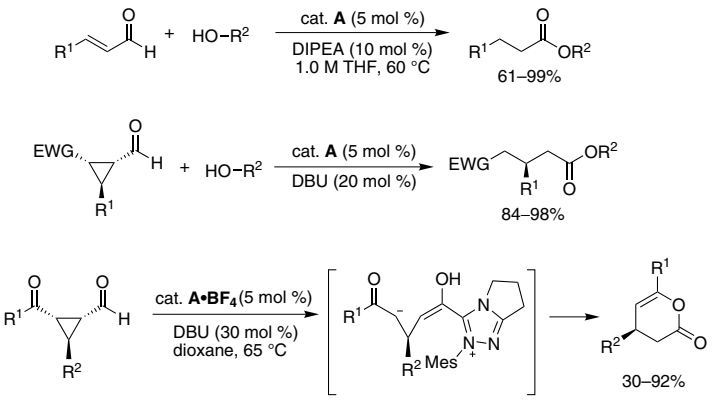
Although a number of azolium precatalysts can be used for redox esterification reactions of α-functionalized aldehydes, the *N*-mesityl or *N*-pentafluorophenyl substituted triazolium salts usually give superior results. A rapidly growing body of literature on these reactions has established that almost any aldehyde with an α-leaving group or reversible functionality serves as a substrate for NHC-catalyzed redox esterifications. The *N*-mesityl substituted catalyst is particularly suited for redox reaction of α,β-unsaturated aldehydes (**Scheme 19**).[16] Other applications include the opening of enantioenriched formyl cyclopropanes to generate esters[34] or dihydropyranones reported by You and coworkers.[35]



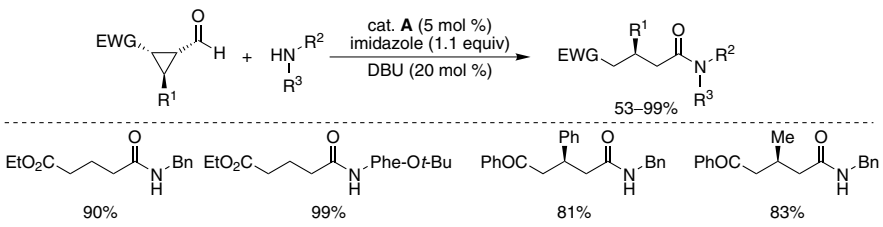
Scheme 17. Formation of esters from α,β-epoxyaldehydes.



Scheme 18. Formation of esters from α-bromoaldehydes.



Scheme 19. Redox reactions promoted by catalyst **A**.



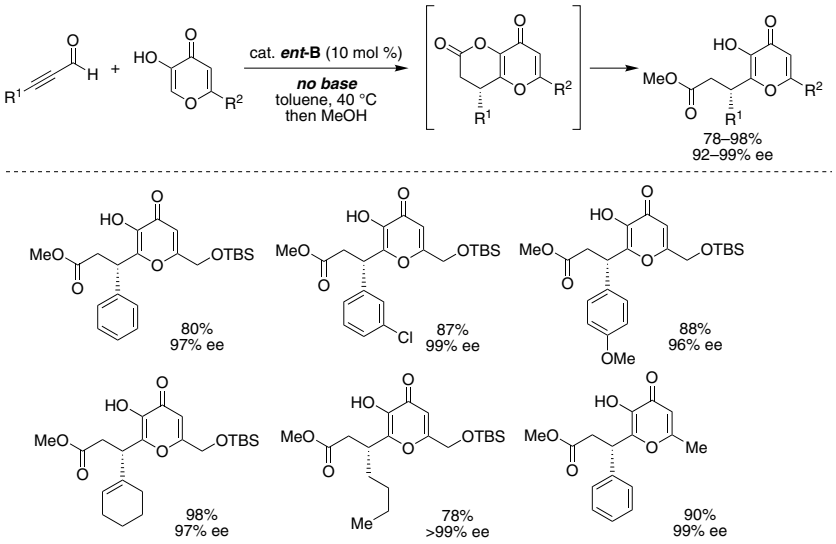
Scheme 20. Redox amidations.

A curious finding of both our group and several others is the reluctance of catalytically generated acyl azoliums to undergo reactions with amines to form amides. This property can be exploited for the chemoselective acylation of alcohols in the presence of amines. The origin of this unusual reactivity lies in the unique properties of the acyl azoliums themselves, which do not readily react with amines to form amide products.[36] Successful NHC-catalyzed amidations do occur with the addition of suitable co-catalysts. In our hands, we have found that the addition of imidazole or similar triazoles make catalytic amidations of α-functionalized aldehydes possible, via the intermediacy of an acyl imidazole that reacts with the amine (**Scheme 20**).[37] Similar chemistry using HOAt as the co-catalytic acylating agent was reported simultaneously by Rovis.[38]

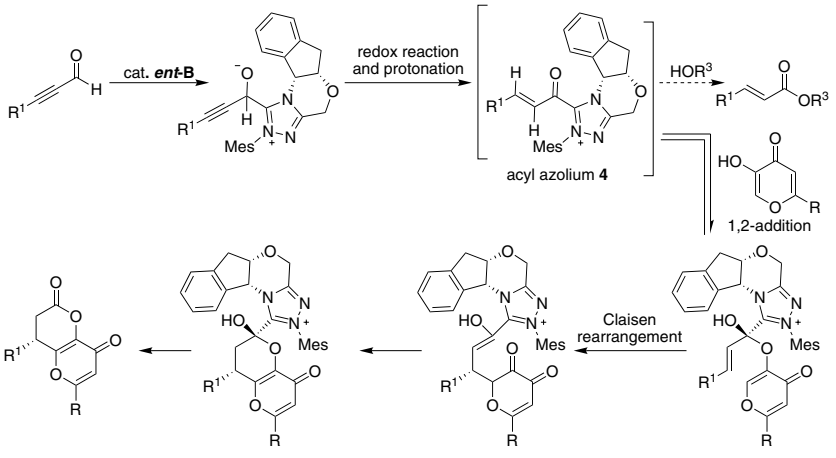
7. Catalytic Annulations by NHC-Catalyzed Claisen Rearrangements

The combination of a chiral N-heterocyclic carbene catalysts and an ynals should lead to the formation of an α,β-unsaturated acyl azolium that may act as an electrophile, representing a completely different activation mode than the acyl anion, homoenolate, ester enolate, or activated carboxylate equivalents discussed so far. Using the identical chiral catalyst, we succeeded in identifying conditions for the selective generation of such intermediates and their use in annulation reactions with enolic substrates, such as kojic acid derivatives (**Scheme 21**).[39]

Our initial work focused on kojic acids as substrates due to their known synthetic utility, but similar conditions give annulation products from pyruvates in excellent yields and selectivities. Recently reported chemistry from other groups



Scheme 21. Enantioselective annulations of ynals and kojic acids.



Scheme 22. Mechanism of Claisen rearrangements.

using 1,3-dicarbonyls as nucleophiles are likely to proceed via a similar mechanism and should be amenable to enantioselective catalysis with chiral catalyst **B** or its relatives.[40] The reactions may also be conducted by starting from the α,β-unsaturated aldehyde and a stoichiometric oxidant with no effect to the observed enantioselectivities.[39]

The mechanism of this reaction is also of considerable interest. Although we initially believed the α,β-unsaturated acyl azolium **4** would be an excellent Michael acceptor, we have been unsuccessful in adding any nucleophiles other than enolates or MeOH/water. This led us to extensively investigate the detailed mechanism revealing an NHC-catalyzed Coates-Claisen rearrangement as the key step. This mechanistic postulate rationalizes the exceptional enantioselectivities observed in this reaction (**Scheme 22**).

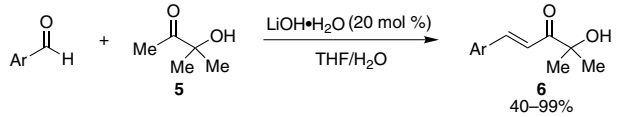
8. α'-Hydroxyenones as Enal Surrogates

The majority of the reaction described in this review use α,β-unsaturated aldehydes as starting materials. Although not obscure compounds, the vast majority of substrates require multiple steps for their preparation. This is particularly true of the highly desired heteroaromatic substrates for which the methods of enal synthesis are complicated by the presence of basic functionality.

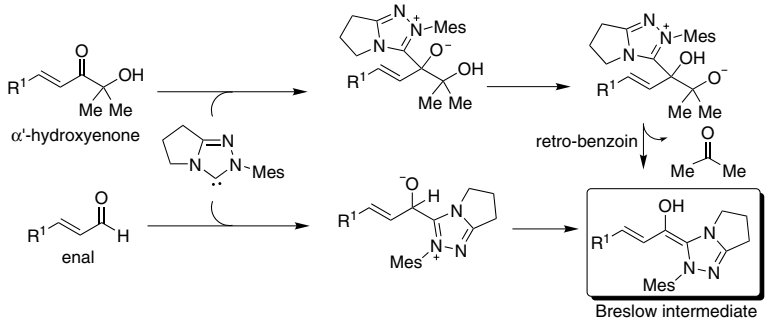
In order to improve the scope of the NHC-catalyzed reactions and expand the range of products that may be prepared with these methods, we have sought readily prepared, bench stable surrogates for aldehydes reaction partners. For ester enolate equivalents, the α-chloroaldehyde bisulfite adducts are ideal,[21] but these cannot be used for reactions involving homoenolate equivalents.

We have therefore developed α'-hydroxyenones **6** as readily prepared surrogates for α,β-unsaturated aldehydes.[41] These substrates can be prepared on a multigram scale from commercially available ketone **5** and aromatic aldehydes (**Scheme 23**).

In the presence of an N-heterocyclic carbene, the α'-hydroxyenones undergo identical reactions as the corresponding α,β-unsaturated aldehydes. In this case, the key reactive intermediates are formed by a retro-benzoin reaction of the initial NHC-ketone adduct (**Scheme 24**).[42]



Scheme 23. Base catalyzed aldol reactions of α'-hydroxyenones synthesis.



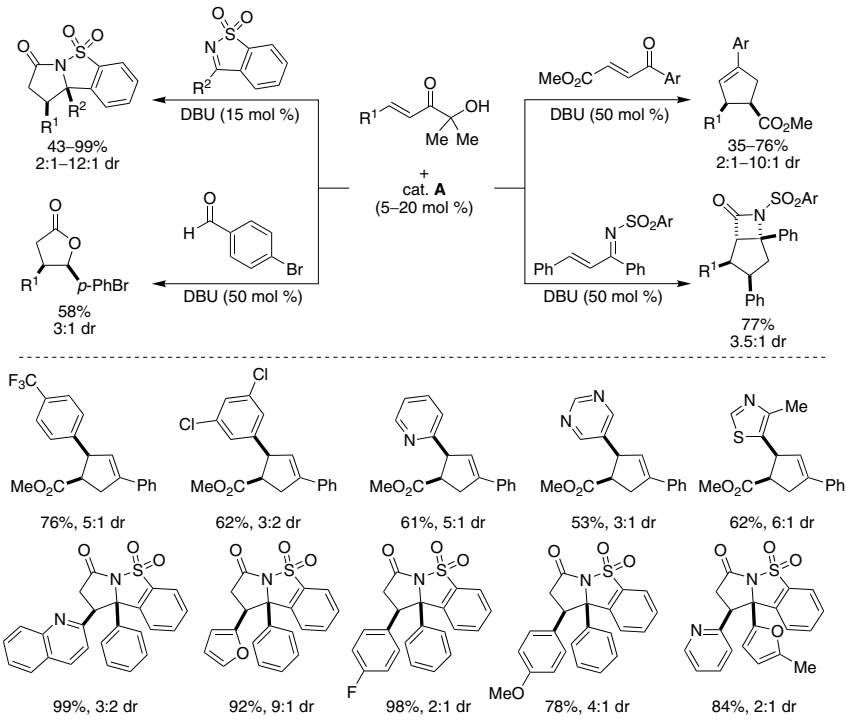
Scheme 24. Generations of Breslow intermediate from α'-hydroxyenones and enals.

These substrates are particularly well suited for the synthesis of cyclopentenes and lactams, with selected examples shown in **Scheme 25**. Due to the increased steric demands of the ketone substrates, these reactions work best with achiral triazolium precatalyst **A**. We therefore highly recommend these conditions for the preparation of racemic mixtures and the preparation of small libraries. Should the enantiopure compounds be needed, they can be prepared with chiral catalysts **B** and ***ent*-B** from the α,β-unsaturated aldehyde.

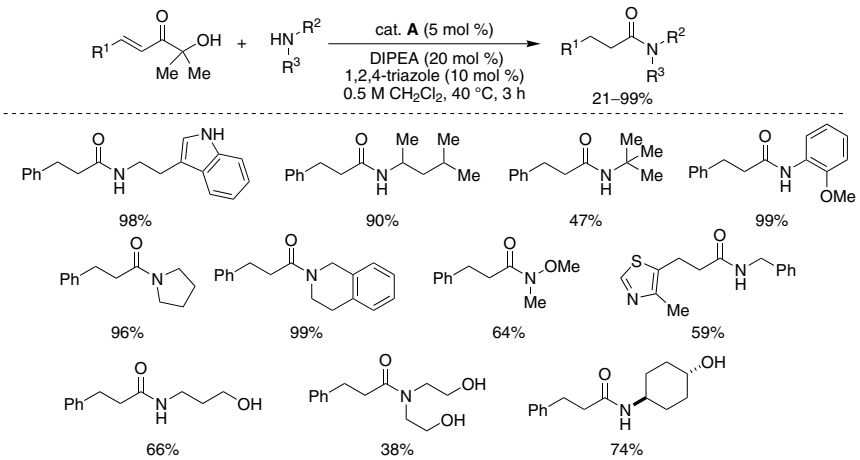
The α'-hydroxyenones are also outstanding substrates for NHC-catalyzed amidations in combination with 1,2,4-triazole as a co-catalyst.[43] Unlike most amidation conditions that require excess amounts of coupling reagents and generate a large amount of waste, these conditions affect catalytic amidations with no products other than acetone and only substoichiometric quantities of reagents. Selected examples are shown in **Scheme 26**.

9. Conclusions

In just four years since the initial report, *N*-mesityl substituted chiral triazolium salts have proven to be one of the most versatile and selective catalysts known. In addition to the remarkable range of products they may be used to construct, they are notable for their high stability, mild reaction conditions (20–40 °C), and tolerance to air and water. A single chiral catalysts work well for nearly all of the reactions reported to date. For a few NHC-catalyzed reactions for which **B** and ***ent*-B** give inferior enantioselectivities, a number of new chiral scaffolds are emerging. Notable, all of these structures maintain the essential *N*-mesityl triazolium core that has proved to be necessary for both reactivity and selectivity in these new generations of N-heterocyclic carbene catalyzed reactions. The commercial availability of these catalysts should encourage the discovery of even more new reactions and applications of the complex, enantiopure products they afford.



Scheme 25. NHC catalyzed annulations using α'-hydroxyenones.



Scheme 26. Catalytic amidation with α'-hydroxyenones.

References

1 F. Wöhler, J. von Liebig, *Annalen der Pharmacie* **1832**, *3*, 249–282.
2 A. Lapworth, *J. Chem. Soc., Trans.* **1903**, *83*, 995–1005.
3 T. Ukai, R. Tanaka, S. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296–300.
4 General review: R. Kluger, K. Tittmann, *Chem. Rev.* **2008**, *108*, 1797–1833.
5 H. W. Wanzlick, E. Schikora, *Angew. Chem.* **1960**, *72*, 494.
6 General review: H. Stetter, H. Kuhlmann, in *The Catalyzed Nucleophilic Addition of Aldehydes to Electrophilic Double Bonds*, John Wiley & Sons, **1991**, Vol. 40, pp 407–496.
7 General review: D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857–7870.
8 R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
9 (a) R. L. Knight, F. J. Leeper, *Tetrahedron Lett.* **1997**, *38*, 3611–3614. (b) R. L. Knight, F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893.
10 (a) D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217–1221. (b) D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899–1902.
11 M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725–5728.
12 D. Enders, U. Kallfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743–1745.
13 M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299.
14 H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3492–3494.
15 General review: (a) J. Moore, T. Rovis, Carbene Catalysts. In *Topics in Current Chemistry*, Springer Berlin, Heidelberg, **2009**, Vol. 291, pp 77–144. (b) F. Glorius, K. Hirano, Nucleophilic Carbenes as Organocatalysts. In *Ernst Schering Found*, Springer Berlin, Heidelberg, **2008**, Vol. 2, pp 159–181.
16 S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873–3876.
17 M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.
18 J. R. Struble, J. W. Bode, *Org. Synth.* **2010**, *87*, 362–376.
19 J. R. Struble, J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2008**, *10*, 957–960.
20 M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089.
21 M. He, B. J. Beahm, J. W. Bode, *Org. Lett.* **2008**, *10*, 3817–3820.
22 J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Nat. Acad. Sci. U.S.A.* **2010**, *107*, 20661–20665.
23 E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3107–3110.
24 S. Kobayashi, T. Kinoshita, H. Uehara, T. Sudo, I. Ryu, *Org. Lett.* **2009**, *11*, 3934–3937.
25 S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371.
26 M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131–3134.
27 M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266–17267.
28 M. He, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 418–419.
29 J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2009**, *11*, 677–680.
30 P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521.
31 K. Y. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127.
32 N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519.
33 H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 2860–2861.
34 S. S. Sohn, J. W. Bode, *Angew. Chem. Int. Ed.* **2006**, *45*, 6021–6024.
35 G.-Q. Li, L.-X. Dai, S.-L. You, *Org. Lett.* **2009**, *11*, 1623–1625.
36 (a) K. Daigo, L. Reed, *J. Am. Chem. Soc.* **1962**, *84*, 659–662. (b) T. C. Owen, A. Richards, *J. Am. Chem. Soc.* **1987**, *109*, 2520–2521. (c) T. C. Owen, J. N. Harris, *J. Am. Chem. Soc.* **1990**, *112*, 6136–6137.
37 J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.
38 H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797.
39 J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810–8812.
40 (a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177. (b) Z. Q. Zhu, J. C. Xiao, *Adv. Synth. Catal.* **2010**, *352*, 2455–2458. (c) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266–9269.
41 (a) G. G. King, J. V. Karabinos, *J. Chem. Eng. Data* **1968**, *13*, 565–566. (b) C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943. (c) M. Reiter, H. Turner, R. Mills-Webb, V. Gouverneur, *J. Org. Chem.* **2005**, *70*, 8478–8485.
42 P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714–8718.
43 P.-C. Chiang, Y. Kim, J. W. Bode, *Chem. Commun.* **2009**, 4566–4568.

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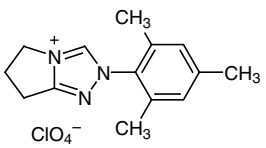
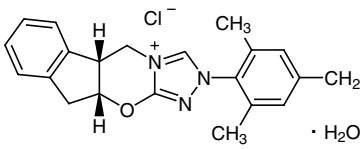
Contribution Related Compounds

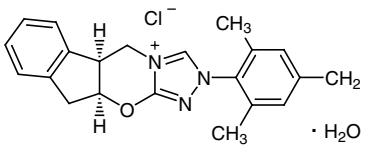
Bode Catalysts



6,7-Dihydro-2-(2,4,6-trimethylphenyl)-5*H*-pyrrolo[2,1-*c*]-1,2,4-triazolium Perchlorate
100mg [D3982]



Bode Catalyst 2
Monohydrate
100mg [D3983]

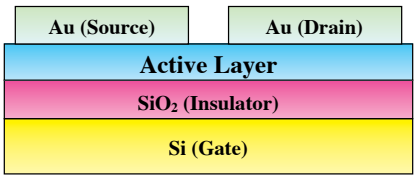


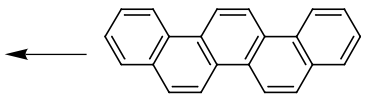
Bode Catalyst 1
Monohydrate
100mg [D3984]

New Organic Functional Material "Picene"

P1893 Picene (purified by sublimation) (1) 100mg, 1g

Field-effect tansistor with thin films of Picene





1

T_c values / metal (K and Rb) and the doping rate

Alkali metal (M)	Metal content (M / 1)	T_c (K)
K	2.9	7
K	**3.3**	**18**
Rb	3.1	7

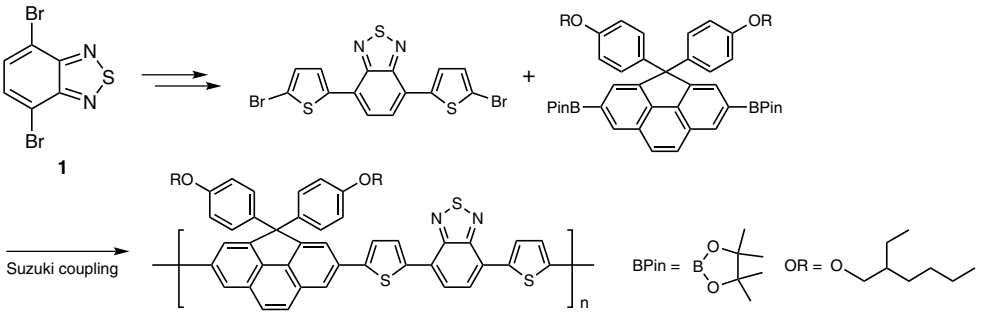
Picene (**1**), whose benzene rings are condensed in a w-shaped, is an aromatic hydrocarbon compound. Recently, Kubozono *et al.* have reported an efficiency modification of Field-effect transistors (FETs) with **1**. Applying **1** into the active layer of FETs resulted in the field-effect mobility value (μ value) being measured 1.1 $cm^2V^{-1}s^{-1}$. Furthermore, the μ value is improved up to 1.75 $cm^2V^{-1}s^{-1}$ after exposure to O_2 atmosphere for 70 hours. This result showed that the modified FET is an O_2-assisted devise, as well as having stability against O_2.[1] In addition, Kubozono *et al.* have also reported the superconductivity of **1** which was intercalated with alkaline metals, such as potassium and rubidium. The T_c (superconducting transition temperature) was 18 K (–255 °C) when **1** was doped with 3.3 equivalents of potassium (based on **1**). This value is the highest one ever for simple and typical organic compounds.[2]

References

1) Air-assisted high-performance field-effect transistor with thin films of picene
H. Okamoto, N. Kawasaki, Y. Kaji, Y. Kubozono, A. Fujiwara, M. Yamaji, *J. Am. Chem. Soc.* **2008**, *130*, 10470.
2) Superconductivity in alkali-metal-doped picene
R. Mitsuhashi, Y. Suzuki, Y. Yamanari, H. Mitamura, T. Kambe, N. Ikeda, H. Okamoto, A. Fujiwara, M. Yamaji, N. Kawasaki, Y. Maniwa, Y. Kubozono, *Nature* **2010**, *464*, 76.

Building Block for Photovoltaic Device Polymers

D3842 4,7-Dibromo-2,1,3-benzothiadiazole (1) 1g, 5g, 25g



2,1,3-Benzothiadiazole is a well-known electron-deficient molecule, which can be conjugated with an electron-rich molecule to form co-polymers with small energy band gaps. Recently, several different co-polymers bearing the benzothiadiazole moiety have been synthesized for organic photovoltaic devices. For instance, Kim *et al.* have reported the synthesis of the co-polymer, which is generated from an electron-rich phenanthrene moiety and an electron-deficient 2,1,3-benzothiadiazole moiety, using **1** as a starting material. According to their results, the bulk heterojunction solar cell composed of this co-polymer and $PC_{71}BM$ gives a power conversion efficiency of 1.12%.

Reference

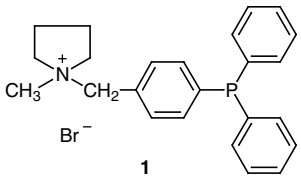
Low-bandgap poly(4*H*-cyclopenta[*def*]phenanthrene) derivatives with 4,7-dithienyl-2,1,3-benzothiadiazole unit for photovoltaic cells
J. Kim, S. H. Park, S. Cho, Y. Jin, J. Kim, I. Kim, J. S. Lee, J. H. Kim, H. Y. Woo, K. Lee, H. Suh, *Polymer* **2010**, *51*, 390.

Ion-supported Triphenylphosphine

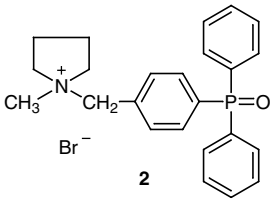
M2103 1-Methyl-1-[4-(diphenylphosphino)benzyl]pyrrolidinium Bromide (1) 1g

1-Methyl-1-[4-(diphenylphosphino)benzyl]pyrrolidinium bromide (**1**) is an air-stable ion-supported triphenylphosphine developed by Togo *et al*. In the halogenation of alcohols and the esterification of carboxylic acids with the Mitsunobu reaction using **1**, co-product, ion-supported triphenylphosphine oxide **2** can be easily separated from the product by ether extraction due to its poor solubility in ether. **2** is recovered by filtration in over 90% yield. After the *O*-methylation of the recovered **2** with dimethyl sulfate and subsequent reduction with $LiAlH_4$, **1** can be regenerated and reused for the same reactions.

1 is also useful as a ligand of metal catalysts for the Mizoroki-Heck reaction and the Sonogashira reaction. The ionic liquid reaction media containing **1** and a palladium catalyst can be reused for the same reactions, maintaining the high yield and the high purity of the products.



1



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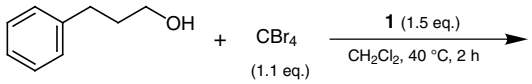
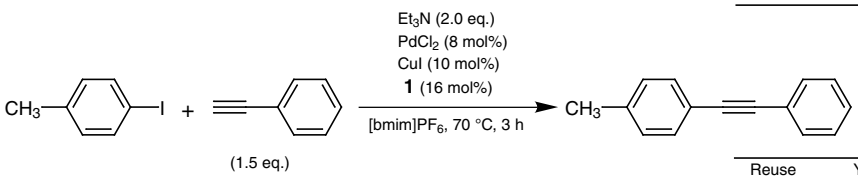


Reuse	Yields (%)	
	1	Ph_3P
0	95	68
1	93	-
2	87	-



Reuse	Yields (%)	
	1	Ph_3P
0	100	91
1	100	92
2	100	99
3	100	76
4	100	41
5	90	18
6	95	-
7	94	-

Typical Procedure: Bromination of alcohols

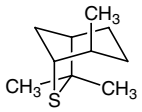
1 (1320 mg, 3.0 mmol) is dried by a vacuum pump for 2 h at 70 °C. To the flask containing **1** is added a solution of 3-phenyl-1-propanol (272 mg, 2.0 mmol) and CBr_4 (729 mg, 2.2 mmol) in dichloromethane (6 mL). The obtained mixture is stirred for 2 h at 40 °C under an argon atmosphere. After the reaction, ether (10 mL) is added and the obtained mixture is stirred for 40 min at room temperature. Then, the mixture is filtered and washed with ether. Removal of the solvent from the filtrates gives 3-phenyl-1-bromopropane in a crude state. The purity is in the range of 70–75%, due to a co-product, $CHBr_3$. Pure 3-phenyl-1-bromopropane is obtained by short column chromatography on silica gel ($CHCl_3$). Co-product **2** is recovered by the above filtration in 93% yield.

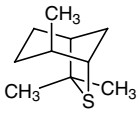
Reference

1) Ion-supported triphenylphosphines and their synthetic utility
Y. Imura, N. Shimojuh, Y. Kawano, H. Togo, *Tetrahedron* **2010**, *66*, 3421.

Useful Chiral Auxiliaries for the Synthesis of Chiral Oxiranes

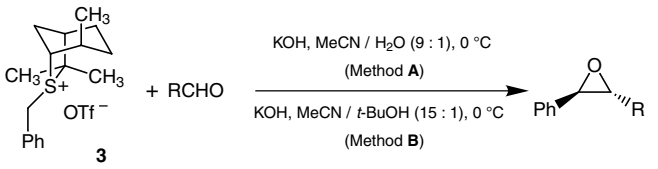
T2578 (1*R*,4*R*,5*R*)-4,7,7-Trimethyl-6-thiabicyclo[3.2.1]octane (**1**) 1g, 5g
T2579 (1*S*,4*S*,5*S*)-4,7,7-Trimethyl-6-thiabicyclo[3.2.1]octane (**2**) 1g, 5g


1


2

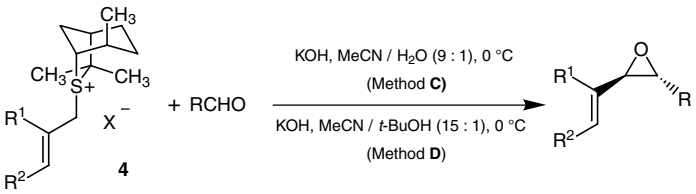
Aggarwal *et al.* have reported an asymmetric synthesis using the sulfur ylides generated *in situ* by treating the sulfonium salts **3** and **4** prepared from (1*R*,4*R*,5*R*)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane (**1**), with bases. According to their results, the reactions of **3** with aldehydes and imines afford the corresponding chiral oxiranes and aziridines, respectively, in high yields with diastereo- and enantioselectivities.[1] On the other hand, the reactions of **4** with aldehydes also give excellent yields of the corresponding α,β-unsaturated oxiranes with perfect stereoselectivities.[1] Moreover, this methodology was also successfully applied to the total synthesis of alkaloids, such as quinine.[1]

Thus, **1** and **2** are useful chiral auxiliaries applicable to the synthesis of various oxiranes and aziridines *via* sulfur ylides.



3

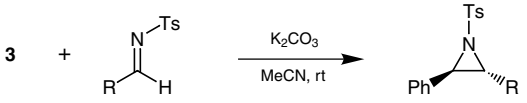
R	Method	Yield (%)	*d.r.*	*e. r.*
Ph	**A**	77	>95 : 5	99 : 1
(*E*)-PhCH=C(Me)	**A**	84	>95 : 5	98 : 2
c-C_6H_{11}	**B**	62	93 : 7	99 : 1
n-C_4H_9	**B**	56	91 : 9	99 : 1



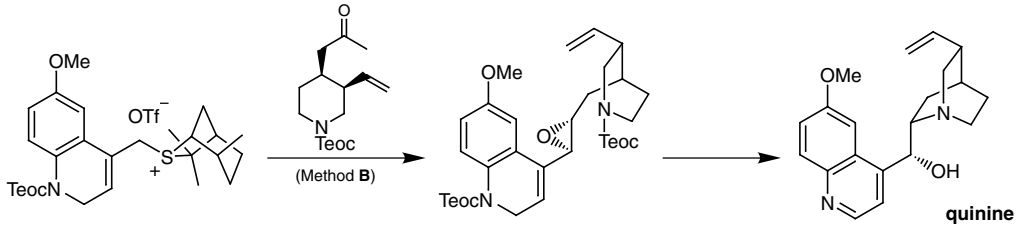
4

R^1	R^2	R	Method	Yield (%)	*d.r.*	*e. r.*
Me	Ph	Ph	**C**[a]	97	>95 : 5	99 : 1
Me	H	Ph	**C**[b]	80	>95 : 5	99 : 1
Me	Ph	*c*-C_6H_{11}	**D**[a]	77	>95 : 5	98 : 2
Me	H	*c*-C_6H_{11}	**D**[b]	77	>95 : 5	97 : 3

[a] X = BF_4. [b] X = OTf.



R	Yield (%)	*trans/cis*	*e. r.*
Ph	72	85 : 15	99 : 1
p-ClC_6H_4	65	75 : 25	99 : 1
p-$MeOC_6H_4$	80	83 : 17	99 : 1
(*E*)-PhCH=CH	78	>99 : 1	98 : 2

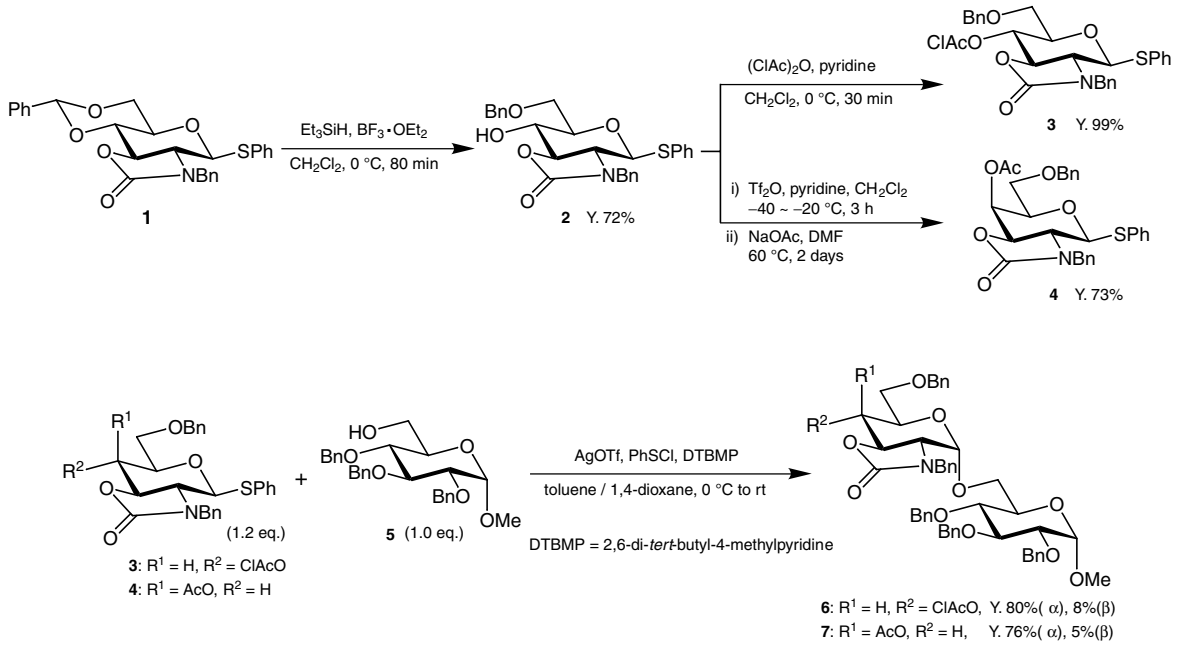


Reference

1) Practical and highly selective sulfur ylide mediated asymmetric epoxidations and aziridinations using an inexpensive, readily available chiral sulfide
O. Illa, M. Arshad, A. Ros, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 1828.

Glycosyl Donor

P1762 Phenyl *N*-Benzyl-2-amino-4,6-*O*-benzylidene-2-*N*,3-*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (1) 1g

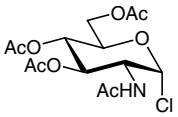


Phenyl *N*-benzyl-2-amino-4,6-*O*-benzylidene-2-*N*,3-*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**1**) is a glycosyl donor developed by Mababe *et al.*, which is used as a building block for 1,2-*cis* glycosidic bond formation of an amino sugar. For example, reductive benzylidene acetal ring opening of **1** gives **2**. Subsequently, **2** is converted either to glucosamine derivative **3** *via* chloroacetylation or to galactosamine derivative **4** *via* stereoinversion and acetylation. **3** or **4** react with glycosyl acceptor **5** to give disaccharide **6** or **7**, respectively, with high α-selectivity. As amino sugars having 1,2-*cis* glycosidic bonds exist in many bioactive sugar chains such as heparin, application of these donors to bioactive oligosaccharide synthesis is promising.

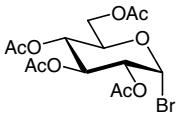
Reference

1) Selective α-glycosylation and one-pot oligosaccharide synthesis involving 1,2-*cis*-glycosylation
S. Manabe, K. Ishii, Y. Ito, *J. Am. Chem. Soc.* **2006**, *128*, 10666.

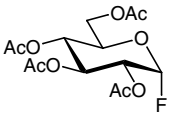
Glycosyl Donors



2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl Chloride
1g, 5g [A1416]



2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Bromide (stabilized with $CaCO_3$)
5g [T1961]



2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl Fluoride
1g [T1995]

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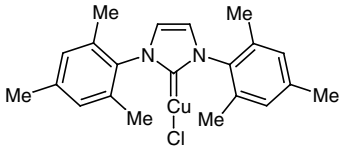
Keyword is "Glycosylation".

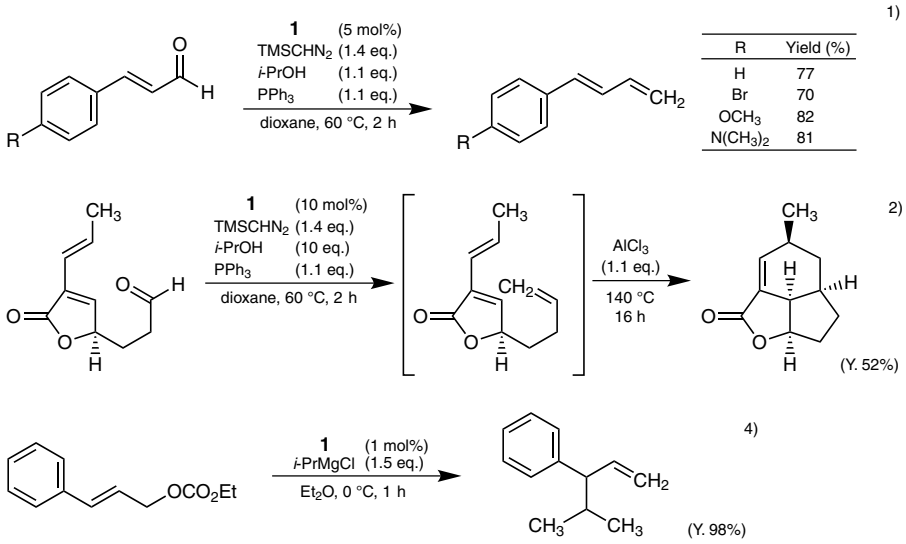
(IMes)-copper Complex for Methylenation and Grignard Reactions

C2422 Chloro(1,3-dimesitylimidazol-2-ylidene)copper(I) (1) 200mg, 1g

Chloro(1,3-dimesitylimidazol-2-ylidene)copper(I) (**1**) is an effective catalyst for the methylenation of a variety of aliphatic and aromatic aldehydes and ketones with trimethylsilyldiazomethane and triphenylphosphine.[1)] The methylenation reaction is applied to a one-pot methylenation-Diels–Alder cyclization,[2)] and a one-pot methylenation-intramolecular Heck reaction.[3)] The complex **1** also catalyzes the allylic substitution reactions with Grignard reagents.[4)]



1
(IMes)-Cu complex



Typical Procedure[1)] (R = H):
To a solution of **1** (20.2 mg, 0.050 mmol) and triphenylphosphine (288 mg, 1.10 mmol) in dioxane (10 mL) at 25 °C is added 2-propanol (84 μL, 1.1 mmol) followed by *trans*-cinnamaldehyde (125 μL, 1.00 mmol) and the trimethylsilyldiazomethane solution (1.4–2.0 mmol) under inert atmosphere. The resulting mixture is then heated at 60 °C for 2 h. Afterward, 3% H_2O_2 (10 mL) is added and the organic layer is extracted with ether (3 x 20 mL). The combined organic layers are washed with brine (2 x 20 mL) and dried over $MgSO_4$. The filtrate is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (eluent: 1% EtOAc/hexanes) to give 1-phenyl-1,3-butadiene (100 mg, Y. 77%) as a colorless oil.

References

Copper-catalyzed methylenation reaction
1) H. Lebel, M. Davi, S. D.-González, S. P. Nolan, *J. Org. Chem.* **2007**, *72*, 144.
2) H. Lebel, M. Parmentier, *Org. Lett.* **2007**, *9*, 3563.
3) H. Lebel, C. Ladjel, L. Bréthous, *J. Am. Chem. Soc.* **2007**, *129*, 13321.
4) S. Okamoto, S. Tominaga, N. Saino, K. Kase, K. Shimoda, *J. Organomet. Chem.* **2005**, *690*, 6001.

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